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Stereoselective Preparation of Primary (*E*)-Allylic Amines by the Reaction of Tantalum-Alkyne Complexes with Metallo-Imines

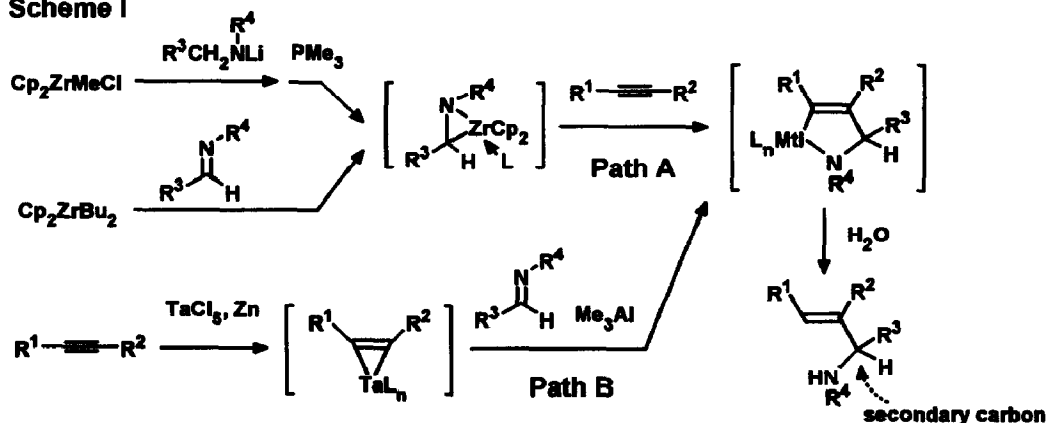
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Abstract: Treatment of tantalum-alkyne complexes with lithio-imines at 25–50 °C for several hours in the presence of Me₃Al gives primary (*E*)-allylic amines having adjacent tertiary carbons in good to excellent yields.

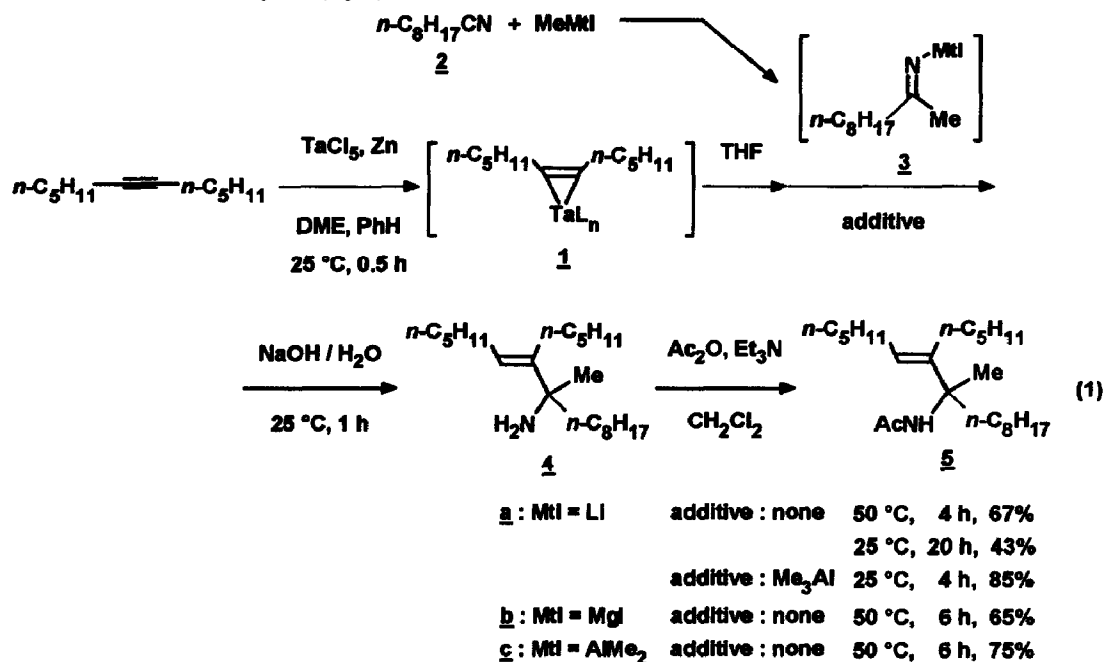
Organometallic compounds of group 5 metals have been found to be excellent tools for use in organic syntheses.^{1,2} The reaction between unsaturated compounds and reagents possessing carbon-metal bonds is a key step in many stereoselective carbon-carbon bond forming processes. These considerations coupled with the importance of nitrogen-containing organic molecules prompted us to study stereoselective synthesis of amines, particularly allylic amines.³ There exist two approaches for the preparation of allylic amines from acetylenes and imine derivatives. These involve the use of early transition metals as activators for the reactions (Scheme 1). In one of the approaches, reported by Buchwald^{4a,b} and Livinghouse,^{4c} (*E*)-allylic amines are prepared in a stereoselective fashion *via* the reaction of zirconocene-imine complexes with acetylenes (path A).⁵ We recently reported an alternative approach to allylic amine derivatives (path B).⁶ This involves the reaction of tantalum-alkyne complexes with *N,N*-dimethylhydrazone (R⁴ = NMe₂) of aldehydes at 45 °C in the presence of Me₃Al to yield (*E*)-allylic hydrazines.

Scheme 1



Because the imine parts of the zirconocene-imine and -hydrazone complexes in path A are limited to those derived from aldehydes, the adjacent carbons of the formed amines must be secondary.⁴ The hydrazone approach (path B) could not be applied to the synthesis of primary hydrazines having tertiary carbons due to

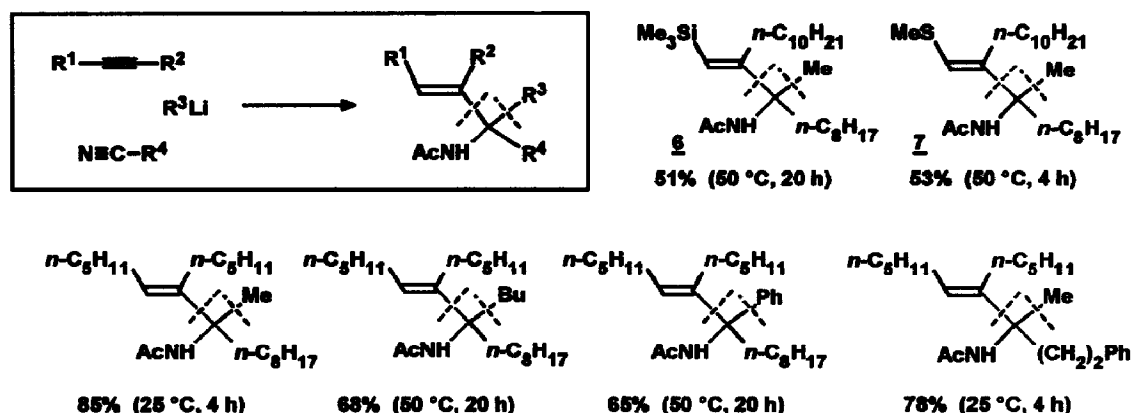
the steric factors.⁶ We have found that the insertion process can be promoted by using a lithio-imine^{7a} as the C=N component,⁸ which is brought close to the tantalum-alkyne complex by ligand exchange.⁹ Addition of nonanenitrile (**2**) to an ethereal solution of methyl lithium at 0 °C for 1 h produced a lithio-imine **3a** (Mtl = Li).^{7a} Treatment of a tantalum-(6-dodecyne) complex **1** with the lithio-imine **3a** at 50 °C for 4 h, followed by alkaline workup produced an allylic amine **4** having *E* configuration. Acetylation of the product gave the amine derivative **5** in 67% yield (eq. 1).



Magnesium-imine **3b** (Mtl = MgI),^{7b} derived by treatment of nonanenitrile with MeMgI (1.2 molar equiv. of **2**) in benzene at 65 °C for 2 h, could be employed in place of the lithio-imine. Heating a mixture of the tantalum complex **1** and magnesium-imine **3b** at 50 °C for 6 h produced **5** in 65% yield after acetylation. The yield was improved and the reaction was accelerated by using aluminum-imine **3c** (Mtl = AlMe₂),^{7c} which was produced by heating the mixture of the nitrile and Me₃Al (4.0 molar equiv. of **2**) in benzene at 80 °C for 24 h. For example, treatment of the complex **1** with the aluminum-imine **3c** at 30 °C for 6 h produced **5** in 75% yield after acetylation. The preparation of the aluminum-imine **3c** requires excess amounts of Me₃Al. Thus, the beneficial effect of Me₃Al on the reaction between the complex **1** and the lithio-imine **3a** was demonstrated in the presence of Me₃Al, the reaction proceeded even at 25 °C and the yield of **5** increased to 85%.¹⁰

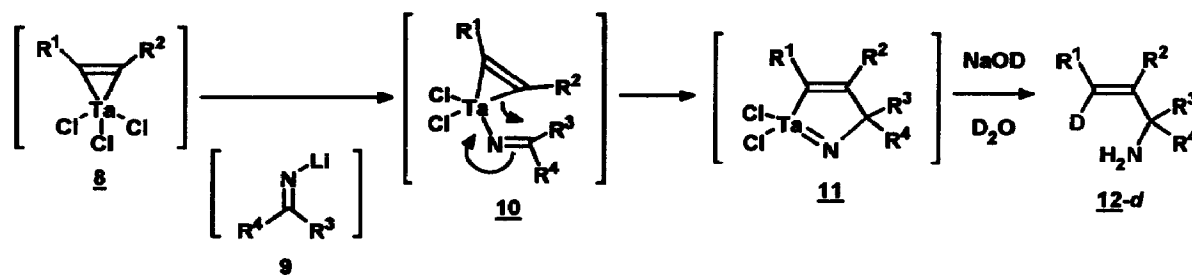
Primary allylic amines having adjacent tertiary carbons were produced from three components, acetylenes, nitriles, and organolithium compounds as shown in Figure 1. The yields were lower and longer reaction times were required in the case of a sterically congested lithio-imines. Thus, the reaction was conducted at 50 °C for 20 h when butyl- or phenyllithium was employed.¹¹ Regioselectivities between the tantalum-unsymmetrical acetylene complexes and the lithio-imines were the same as those between the complexes and aldehydes.^{2e} The new carbon-carbon bond was formed at the less hindered side of the tantalum-alkyne complex in the case of 1-trimethylsilyl-1-alkyne (Fig 1, 6).^{2a} When methylthioacetylene was employed, the carbon-carbon bond was formed at the β-position of the methylthio group (Fig 1, 7).^{2d}

Figure 1



The reaction may be explained by the mechanism shown in Scheme 2. Transmetalation of the lithio-imine **9** with the tantalum-alkyne complex **8** would produce a tantalio-imine **10** containing a tantalacyclopentene. Ring enlargement of **10** would give an azatantalacyclopentene intermediate **11**.¹² Relief of the strain of **10** could be the driving force of this rearrangement to **11**, which can be regarded as metal analog of vinylcyclopropane-cyclopentene rearrangement. Quenching the reaction mixture of **11a** (a: $R^1=R^2=n-C_5H_{11}$, $R^3=Me$, $R^4=n-C_8H_{17}$) with an NaOD solution yielded deuterated amine **12a-d** in 62% yield (deuterium content: 88%).

Scheme 2



Typical procedure for the reaction between an alkyne and a lithio-imine by means of a TaCl₅-Zn system: Low-valent tantalum was prepared from TaCl₅ (0.72 g, 2.0 mmol) and zinc (0.20 g, 3.0 mmol) in DME-benzene (1:1, 10 mL) as reported.^{2d} To the mixture was added at 25 °C a solution of 6-dodecyne (0.17 g, 1.0 mmol) in DME-benzene (1:1, 2 mL) and the mixture was stirred at 25 °C for 30 min. THF (6 mL) was added at 25 °C to the mixture and the resulting mixture was stirred at 25 °C for 15 min. A solution of a lithio-imine in ether-hexane was prepared separately: A solution of nonanenitrile (0.28 g, 2.0 mmol) in ether (1.5 mL) was added into a solution of MeLi (a 1.14 M hexane solution, 1.9 mL, 2.2 mmol) in ether (2 mL) at 0 °C over a period of 5 min and the resulting mixture was stirred at 0 °C for 1 h. To the mixture of tantalum-(6-dodecyne) complex was added the solution of lithio-imine and a benzene solution of Me₃Al (1.0 M, 4.0 mL, 4.0 mmol) at 25 °C. The resulting mixture was stirred at 25 °C for 4 h. Aqueous NaOH solution (15%, 2 mL) was added slowly at 0 °C and the mixture was stirred at 25 °C for an additional 1 h. The deposited solid was removed by filtration with Hyflo-Super Cel[®] and washed with ethyl acetate (3x5 mL). The filtrate and washings were dried over Na₂SO₄ and concentrated. The crude product was passed through short column chromatography on silica gel (ethyl acetate-hexane, 1:10 → ethyl acetate only) and concentrated. The obtained

mixture was acetylated at 25 °C for 1 h with acetic anhydride (2 mL) and Et₃N (2 mL) in CH₂Cl₂ (10 mL). Purification of the mixture by column chromatography on silica gel (ethyl acetate-hexane, 1:3) gave 0.31 g (85% yield) of acetylated allylic amine 5.

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